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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/667,931	09/22/2003	Poh K. Hui	DM-6919 CNT(BMS-2441)	1625

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EXAMINER	
HUYNH, CARLIC K	
ART UNIT	**PAPER NUMBER**
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/667,931	HUI ET AL.	
	Examiner	Art Unit	
	Carlic K. Huynh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-86* is/are pending in the application.

4a) Of the above claim(s) *85-86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08). Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :20 November 2003, 30 June 2004, 14 July 2004, and 4 December 2006.

DETAILED ACTION

Status of the Claims

1. Claims 45-86 are pending in the application, with claims 85-86 having been withdrawn from consideration, in response to the restriction requirement submitted on October 20, 2006. Accordingly, claims 45-84 are being examined on the merits herein.

Election/Restrictions

2. Applicant's election without traverse of the claims of Group I, namely claims 45-84, in the reply filed on November 20, 2006 is acknowledged.

Claims 85-86 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on November 20, 2006.

The election/restriction requirement is deemed proper and is made FINAL.

Information Disclosure Statement

The Information Disclosure Statement submitted on November 20, 2003, June 30, 2004, July 14, 2004, and December 4, 2006 is acknowledged.

Specification

3. The disclosure is objected to because of the following informalities: typographical error. There are numerous instances where the lipid, "1,2-dipalmitoyl-*sn*-glycero-3-phosphotidic,

monosodium salt", is misspelled (page 4 line 21, page 7 line 22, page 8 line 37, page 10 line 12, and page 23 line 12). The lipid should be "1,2-dipalmitoyl-*sn*-glycero-3-phosphotidic acid, monosodium salt".

Appropriate correction is required.

4. The disclosure is objected to because of the following informalities: typographical error. There is a misspelling of the word "solvent" (page 13 line 10).

Appropriate correction is required.

5. The use of the trademark Filamatic® has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

6. Claim 53 is objected to because of the following informalities: step (1) of claim 53 is improperly dependent on claim 1. Claim 1 was cancelled in a Preliminary Amendment filed on October 15, 2003. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 45-46, 48, 50, and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Nyberg et al. (U.S. Patent 5,677,472).

Nyberg et al. disclose methods of preparing phospholipids precipitates comprising mixing a phospholipids blend containing phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin in an organic solvent mixture of polar organic solvent (e.g. methanol) and essential non-polar organic solvent (e.g. toluene), concentrating the solution, then add a second organic solvent of intermediate polarity (e.g. acetone and heptane) to cause precipitation of phospholipids at about 13^{O}-25^{O} C, and drying the precipitate (see example 1, 2, 6, and claim 1). Nyberg et al. specifically indicate separation of phospholipids into different phases (column 5, lines 53-57; example 1, lines 56-67; and example 2).

Regarding claim 50, Nyberg et al. teach warming the non-aqueous solvent system to 25^{O} C, which meets the limitations of the instant claim (example 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 45, 47, 49, 51, 53-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg et al. (U.S. Patent 5, 667,472) in view of Fischer et al. (U.S. Patent 5,840,661), Unger et al. (U.S. Patent 5,585,112), Unger (U.S. Patent 6,416,740), and Senior et al. (Biochimica et Biophysica Acta, 1991, 1062, pp. 77-82).

The teachings of Nyberg et al. are discussed above. Nyberg et al. explicitly indicate similar methods of extracting a phospholipids utilizing suitable solvent systems (column 3, lines 6-15). Nyberg further teaches the precipitation of a phospholipids mixture, "brown phase," by using suitable solvent systems (example 2-3; column 9, lines 54-57). Nyberg et al. also acknowledge the wide use of phospholipids in the medical field (column 1, lines 17-30). Nyberg et al. do not employ methyl t-butyl ether as an intermediate solvent and further fail to prepare and sterilize phospholipids suspensions.

Fischer et al. are solely used to show that methyl t-butyl ether and acetone are art equivalent solvents (column 59, lines 55-60).

Unger et al. teach suitable mixtures of phospholipids including dipalmitoylglycerophosphatidylcholine, dipalmitoylglycerophosphatidic acid, and phosphatidylethanolamine-PEG 5000 in combination with a gaseous perfluoropropane. Unger further uses polyols such as polyethylene glycol in preparing phospholipids suspensions (abstract; columns 2, 10, 12, 22, 25; and examples 1-3).

Senior et al. further teach a dipalmitoylphosphotidylethanolamine (DPPE) covalently coupled to methoxypolyethylene glycol (MPEG 5000) (abstract).

Unger teaches a method for sterilizing phospholipids suspensions (column 52, lines 47-56).

Accordingly, absence the showing of unexpected results, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute Nyberg's acetone with methyl t-butyl ether, because as shown by Fischer et al. such organic solvents are art equivalents. Furthermore, absence the showing of unexpected results, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the phospholipid blend of Nyberg et al., as modified by Fischer et al., in polyols such as polyethylene glycol, as taught by Unger et al., Senior et al., and Unger, and formulate suitable phospholipid suspensions for medical imaging, because such suspensions, as recognized by Nyberg et al. and taught by Unger et al., are readily used in the art of ultrasonic imaging applications.

The motivation to combine the acetone as taught by Nyberg et al. with the methyl t-butyl ether as taught by Fischer et al. is acetone and methyl t-butyl ether are art equivalent organic solvents.

The motivation to combine the phospholipid blend of Nyberg et al. with the phospholipid blend of Fischer et al., Unger et al., Senior et al., and Unger is they are suitable phospholipid suspensions for use in medical imaging such as ultrasonic imaging applications.

Regarding claims 56-57, Unger et al. teach providing a dispersed phospholipids blend solution at 50^{O} C, which meets the limitations of the instant claims (example 4A).

Regarding claims 58-59, Unger et al. teach the ratio of solid phospholipids blend to polyol solvent is 5 mg/mL, which meets the limitations of the instant claims (example 1). It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the ratio of solid phospholipids blend to polyol solvent provided in a composition, according to the guidance set forth in Unger et al., to provide a

composition having the desired ratio of solid phospholipids blend to polyol solvent. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

Regarding claims 68-70, Unger teach lipid aggregates are 200 nm in size and may be as small as 5-10 nm in size, which meets the limitations of the instant claims (column 26, lines 22-23).

Regarding claims 71-72, Nyberg et al. teach heating the aqueous solution to 40^{O} C (example 5). It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the aqueous solution temperature provided in a composition, according to the guidance set forth in Nyberg et al., to provide a composition having the desired aqueous solution temperature. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

Regarding claims 73-74, Unger et al. teach the phase transition temperature is 41^{O} C and the lipid solution temperature is $42\text{-}50^{O}$ C, which meets the limitations of the instant claims (example 8). It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the lipid solution temperature provided in a composition, according to the guidance set forth in Unger et al., to provide a composition having the desired lipid solution temperature. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or

workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

Regarding claims 75-78, Unger teaches filtering a phospholipid suspension through a sterilizing filter (column 52, lines 38-41), filtering using at least 1 filter (column 52, lines 4 and 17-19), the temperature of the filter (column 52, lines 57-59), and the filter pore size of 0.1-5 μm (column 52, lines 38-39), which meet the limitations of the instant claims.

Regarding claims 79-82, Unger teaches dispensing the phospholipid suspension into a vial (column 52, lines 26-29), a perfluorocarbon gas (column 28, line 21), perfluoropropane (column 28, line 26), and the method to exchange gas (column 29, lines 15-16), which meet the limitations of the instant claims.

Regarding claims 83-84, Unger teaches a method of sterilization (column 52, lines 26-29 and 47-56).

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carlic K. Huynh whose telephone number is 571-272-5574. The examiner can normally be reached on Monday to Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ckh

S. Wang

SHENGJUN WANG
Patent Examiner